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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,474	03/05/2001	Kazuo Nagai	084335/0131	1349

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EXAMINER	
BUGAISKY, GABRIELE E	
ART UNIT	PAPER NUMBER
1653	16

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/786,474	NAGAI ET AL.	
	Examiner	Art Unit	
	Gabriele E. BUGAISKY	1653	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10-12 and 14-43* is/are pending in the application.

4a) Of the above claim(s) *10-12 and 14-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 20-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response of 9/3/2002 is acknowledged. Claims 5-9 and 13 have been cancelled and new claims 20-43 have been submitted.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the claims of Group II do not require additional search nor do they place a serious burden on the Examiner.. This is not found persuasive because the Examiner does not limit herself to a mere sequence search. With respect to possible rejoinder, such will occur only if the scope of any process claims is identical to that of any allowable claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-12 and 14-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

Except for US 4681847, all documents supplied with the PTO-1449 have no English translation. The Examiner has no knowledge of Japanese; such documents have only been considered to the extent possible from the brief summary provided by Applicants' representative.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Novel gene conferring lysozyme insensitivity to *Corynebacterium*.

Claim Objections

Claims 20, 26 and 30 are objected to because of the following informalities:

The final line e of claim 20 recites "lysozyine"; this presumably should be "lysozyme".

In claim 26: presumably, "C*ozynebacterium*" should be "*Corynebacterium*".

In claim 30: "Corynebacterium glutamicum" is not italicized. The Examiner presumes Applicant wishes this claim to be consistent with all other claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 , 20-22 , 24-26 and 28-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "fragment" as taught by page 6, line 5 of specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 23, 27, 31, 35 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel microorganisms (FERM BP-6479). Since the microorganism is essential to the claimed invention it must be obtainable by a repeatable method

set forth in the specification or otherwise be readily available to the public. If the microorganism is not so obtainable or available, the requirements of 35 U.S.C. §112 may be satisfied by a deposit of the microorganism. The specification does not disclose a repeatable process to obtain the microorganism and it is not apparent if the microorganism is readily available to the public. **It is noted that applicants have deposited the organism** (page 22, lines 27-32) **but there is no indication in the specification as to public availability.** If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) the deposit will be replaced if it should ever become inviable.

Claims 1-3, 20-22, 24-26, 28-30, 32-34, 36-38 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA encoding the protein of SEQ ID NO:2, which upon expression confers lysozyme insensitivity to strains that are lysozyme sensitive, , constructs containing this DNA and a method of making the protein of SEQ ID NO:2 does not reasonably provide enablement for any DNA which encodes a mutated protein derived from SEQ ID NO:2, or DNA which encodes a protein which has a certain degree of sequence similarity to SEQ ID NO:2 or DNA which hybridizes to DNA encoding SEQ ID NO:2 and encodes a protein that upon expression confers lysozyme insensitivity to strains that are lysozyme sensitive. Similarly , constructs containing such DNA and methods of making these other proteins cannot be enabled. . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice invention commensurate in scope with these claims.

In *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). the issue of enablement in molecular biology was considered. There are eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. Although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

Most , simply, with respect to claims3 and claims dependent from it, a DNA strand cannot both hybridize to the coding strand of protein XYZ AND encode protein XYZ, unless

the DNA is plaindromic. There is no evidence on the record that the DNA encoding SEQ ID NO:2 is palindromic.

The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNAs encoding proteins broadly encompassed by the claims. Applicants have presented but a single species, yet claim a genus of DNA encoding a polypeptide that confers lysozyme insensitivity , a genus of DNA encoding proteins bearing 60% homology to a polypeptide that confers lysozyme insensitivity or a DNA that hybridizes and encoded a polypeptide that confers lysozyme insensitivity. The specification is directed toward the sequences encoding a *Corynbacterium glutamicum* protein witch that confers lysozyme insensitivity to *Corynbacterium* and does not address homologs or mutants. With respect to the DNA of Claim 1, for example, by sufficient mutation deletion and substitution, one might eventually obtain a DNA encoding a polypeptide that confers lysozyme insensitivity , wherein the protein have no relation to SEQ ID NO:2 other than a shared functional characteristic. The specification is silent on how one might achieve such a DNA.

Applicants have provided no means of obtaining any such DNA & have offered but an invitation to experiment in order to do so. The instant fact pattern closely resembles that in *Ex parte Maizel*, 27 USPQ2d 1662 (BPAI 1992). In *Ex parte Maizel*, the claimed invention was directed to compounds which were defined in terms of function rather than sequence (i.e., "biologically functional equivalents"). The only disclosed compound in *Ex parte Maizel* was the full length, naturally occurring protein, whereas in the instant case, but a single full length gene encoding a specific protein is disclosed. The Board found that there was no reasonable correlation between the scope of exclusive right desired by Appellant and the scope of

enablement set forth in the patent application. Even though Appellant in *Ex parte Maizel* urged that the biologically functional equivalents would consist of proteins having amino acid substitutions wherein the substituted amino acids have similar hydrophobicity and charge characteristics such that the substitutions are "conservative" and do not modify the basic functional equivalents of the protein, the Board found that the specification did not support such a definition, and that the claims encompassed an unduly broad number of compounds. Such is the instant situation. Clearly, a single fully disclosed sequence does not support claims to DNA encoding any protein with a certain degree of sequence identity, given the lack of guidance regarding what sequences define the lysozyme insensitivity properties of SEQ ID NO: 2.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 20-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites "hybridizing. . . under stringent conditions". This is deemed to be indefinite because there are no art recognized stringent hybridization conditions. Rather, these conditions must be empirically determined for each individual DNA. The example of a stringent condition on page 4, lines 11-17 of the specification is noted; however, the example is non-limiting.

It is unclear what is meant by 'sensitivity" or "insensitivity to lysozyme" in claims 1-4, 20-23 and 40-43. Is it e.g., formation of protoplasts upon dissolution of the cell wall or , e.g., ability to grow in the presence of lysozyme.?

Claims 20-23 and 42-43 recite " . . . giving an insensitivity to 100 μg/ml lysozyme to a mutant of *Corynebacterium glutamicum* and having a sensitivity to not more than 50 μg/ml lysozyme" is quite confusing. If a strain is sensitive to 50 μg/ml lysozyme, then would it not *a priori* also be sensitive to more than that amount? As best as the Examiner can determine, the intent of the above phrase is "conferring resistance to 100 μg/ml lysozyme to a mutant strain of *Corynebacterium glutamicum* that is sensitive to 50 μg/ml lysozyme". What is not stated and thus not clear is that the resistance/sensitivity is measured in cells cultured under the same conditions, as it is known in the art that culture conditions affect the sensitivity of *Corynebacterium* to lysozyme (see, e.g., U.S. patent 4617267, column 3, lines 7-25) "Since cells of microorganisms belonging to the genus Corynebacterium or analogous species thereof when cultivated in a conventional medium are insensitive to a bacteriolytic enzyme such as egg white lysozyme, it is necessary to render them sensitive to such lysozyme prior to use . . . during the log phase cultivation period, penicillin in an amount which does not inhibit or sub-inhibit the growth, usually 0.1-10 U/ml culture liquor, is added to the medium and cultivation is continued for several generations. Lysozyme-sensitive cells are thus obtained."

Claims 24-39 are included in this rejection as they depend from the above claims and do not clarify the ambiguity.

Allowable Subject Matter

An isolated and purified DNA encoding SEQ ID NO:2, which, upon expression, confers to *Corynebacterium* the ability to grow in medium containing 100 µg/ml lysozyme is deemed free of the prior art. The closest prior art would appear to be US 4, 681, 847, which describes stable strains of *C. glutamicum* that are ultra sensitive to the action of lysozyme and form protoplasts under low concentrations of the enzyme. There is, however, no nexus between these strains and the specific cloned DNA fragment of the instant invention. At best, the patent presents one with an invitation to experiment to try to isolate the gene(s) responsible for the changes in lysozyme sensitivity in the patented strains.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (703)308-4201. The examiner can normally be reached on Tuesdays and Thursdays 8:15 AM-2:00PM and on Wednesdays and Fridays 8:15 AM-1:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher SF Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are 703 308-4242 for regular communications and 703 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708 308-0196.

Gabriele E. BUGAISKY
Primary Examiner
Art Unit 1653

November 17, 2002

GABRIELLE BUGAISKY
PRIMARY EXAMINER